National Toxicology Program
Toxicity Report Series
Number 70

NTP Technical Report on the Toxicity Studies of

p-tert-Butylcatechol

(CAS No. 98-29-3)

Administered in Feed to F344/N Rats and B6C3F$_1$ Mice

November 2002

U.S. Department of Health and Human Services
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Toxicity Study Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals.

These studies are designed and conducted to characterize and evaluate the toxicologic potential of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Toxicity Study Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's toxic potential.

Details about ongoing and completed NTP studies are available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov. Abstracts of all NTP Toxicity Study Reports and full versions of the most recent reports and other publications are available from the NIEHS' Environmental Health Perspectives (EHP) http://ehp.niehs.nih.gov (800-315-3010 or 919-541-3841). In addition, printed copies of these reports are available from EHP as supplies last. A listing of all the NTP Toxicity Study Reports printed since 1991 appears on the inside back cover.

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PEER REVIEW

The draft report on the toxicity studies of *p-tert*-butylcatechol was evaluated by the reviewers listed below. These reviewers serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, reviewers determine if the design and conditions of these NTP studies are appropriate and ensure that this Toxicity Study Report presents the experimental results and conclusions fully and clearly.

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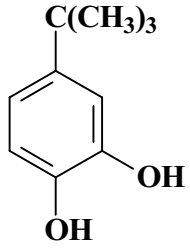
ABSTRACT



p-tert-BUTYLCATECHOL

CAS No. 98-29-3

Chemical Formula: $C_{10}H_{14}O_2$ Molecular Weight: 166.2

Synonyms: 1,2-Benzenediol, 4-(1,1-dimethylethyl-(9CI); 4-*tert*-butyl-1,2-benzenediol; 4-*tert*-butylcatechol; 4-*tert*-butyl-(8CI); 4-*tert*-butyl-1,2-dihydroxybenzene; 1,2-dihydroxy-4-*tert*-butylbenzene; PTBC; TBC; 4-TBC

p-tert-Butylcatechol is used as an antioxidant, stabilizer, and polymerization inhibitor for styrene, butadiene, neoprene, and other olefins and reactive monomers. *p-tert*-Butylcatechol was nominated by the National Cancer Institute and the U.S. Food and Drug Administration for testing based on reports of its increasing levels of production and use and to compare the toxicity of *p-tert*-butylcatechol with that of similar antioxidants, butylated hydroxyanisole and butylated hydroxytoluene, which are added to food. Male and female F344/N rats and B6C3F_1 mice were exposed to *p-tert*-butylcatechol (greater than 99% pure) in feed for 15 days or 14 weeks. Genetic toxicology studies were conducted in *Salmonella typhimurium*, rat bone marrow cells, and mouse peripheral blood erythrocytes.

In the 15-day studies, groups of five male and five female rats and mice were fed diets containing 0, 3,125, 6,250, 12,500, 25,000, or 50,000 ppm *p-tert*-butylcatechol (equivalent to average daily doses of approximately 290 to 2,470 mg *p-tert*-butylcatechol/kg body weight to rats and 590 to 8,200 mg/kg to mice). All animals in the 50,000 ppm groups were killed moribund on day 8 (rats) or by day 7 (mice). Mean body weights of all groups of rats exposed to 6,250 ppm or greater were significantly less than those of the controls. Mean body weights of male mice exposed to 12,500 or 25,000 ppm and of 25,000 ppm female mice were significantly less than those of the controls. Female rats, male and female mice in the 25,000 ppm groups, and 12,500 ppm male mice lost weight during

the studies. Feed consumption by exposed rats generally decreased with increasing exposure concentration; feed consumption by exposed mice was similar to that by the controls.

Thymus weights of 25,000 ppm rats and mice were significantly less than those of the controls. Gross findings noted at necropsy included thin carcasses for three male and all female rats in the 12,500 ppm groups and all male and female rats and mice in the 25,000 and 50,000 ppm groups. No exposure-related lesions were observed microscopically.

In the 14-week studies, groups of 10 male and 10 female rats and mice were fed diets containing 0, 781, 1,562, 3,125, 6,250, or 12,500 ppm *p-tert*-butylcatechol (equivalent to average daily doses of approximately 70 to 1,030 mg/kg to rats and 135 to 2,815 mg/kg to mice). All animals survived to the end of the studies. Mean body weights of male rats exposed to 1,562 ppm or greater, female rats exposed to 3,125 ppm or greater, male mice exposed to 12,500 ppm, and female mice exposed to 6,250 or 12,500 ppm were significantly less than those of the controls. Feed consumption by male and female rats in the 6,250 and 12,500 ppm groups at week 1 and the 12,500 ppm groups at week 14 was less than that by the controls; feed consumption by exposed and control mice was similar.

An erythrocytosis, indicated by increased hematocrit values, hemoglobin concentrations, and erythrocyte counts, was observed in 6,250 and 12,500 ppm rats on day 4 and in 12,500 ppm rats on day 22. At these time points, a transient hepatic effect was demonstrated by increases in alanine aminotransferase activities and bile salt concentrations in exposed rats.

In 12,500 ppm male rats, absolute left cauda epididymis, epididymis, and testis weights were decreased by 15%, 10%, and 9%, respectively, compared to the controls. The number of spermatid heads per testis and epididymal sperm motility of male rats in the 12,500 ppm group were significantly less than those of the controls. The numbers of cycling female rats and females with regular estrous cycles were decreased in the 6,250 and 12,500 ppm groups. Exposed groups of females had significantly fewer estrous cycles than did the controls. Estrous cycle length increased with increasing exposure concentration; female rats in the 6,250 and 12,500 ppm groups had significantly longer cycles and spent more time in diestrus and less time in proestrus, estrus, and metestrus than did the controls. Female mice in the 12,500 ppm group had a significantly longer estrous cycle than did the controls.

The incidences of hyperkeratosis of the forestomach epithelium were significantly increased in male and female rats in all exposed groups and in 12,500 ppm female mice. The incidences of hyperplasia of the forestomach epithelium were significantly increased in male and female rats exposed to 3,125 ppm or greater, male mice exposed to 12,500 ppm, and female mice exposed to 6,250 or 12,500 ppm. The severities of the forestomach lesions were

minimal to moderate in male rats and minimal to mild in female rats and in mice. All male rats exposed to 6,250 or 12,500 ppm had minimal cytoplasmic alteration in the liver.

The absorption, distribution, metabolism, and excretion of *p-tert*-butylcatechol following intravenous injection, gavage dosing, or dermal application were determined in male F344/N rats and B6C3F$_1$ mice. The absorption of [^{14}C]-*p-tert*-butylcatechol following gavage dosing or dermal application was high. The percent absorption following dermal application increased with increasing dose. Peak concentrations of [^{14}C]-*p-tert*-butylcatechol equivalents in plasma were reached 1 hour after gavage dosing (200 mg/kg) and 2 hours after dermal application (60 mg/kg); no parent compound was detected in the plasma extracts. Regardless of route of administration, *p-tert*-butylcatechol-derived radioactivity was readily excreted in the urine and was markedly nonpersistent in the tissues. *p-tert*-Butylcatechol was excreted as *p-tert*-butylcatechol sulfate and other polar metabolites that included predominately sulfate conjugates; it was not excreted as the parent compound. One metabolite was determined to be an *O*-methyl-*O′*-sulfate of *p-tert*-butylcatechol.

p-tert-Butylcatechol (10 to 1,000 µg/plate) was not mutagenic in any of several strains of *S. typhimurium* with or without rat or hamster liver S9. Bone marrow micronucleus tests in which 125 to 500 mg/kg *p-tert*-butylcatechol was administered three times by intraperitoneal injection to male rats gave negative results. No increases in the frequencies of micronucleated normochromatic erythrocytes were observed in the peripheral blood of male or female mice administered *p-tert*-butylcatechol in feed for 14 weeks. No significant alteration in the percentage of polychromatic erythrocytes in mouse bone marrow was observed.

In summary, the primary toxicity of *p-tert*-butylcatechol was to the forestomach of rats and mice. In the 14-week study in rats, forestomach toxicity was observed at all exposure concentrations, and the no-observed-adverse-effect level (NOAEL) was not reached for this effect. In the 14-week study in mice, the NOAEL for forestomach toxicity was 1,562 ppm.